Variation in airway diameter

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Summary

Subject of this thesis is the variation in airway diameter. In patients with obstructive airways diseases like asthma and chronic obstructive pulmonary disease (COPD), the airway diameter can change markedly between days and within days and there can be an excessive decrease in lung function over a longer period of time when compared to the course over time in healthy individuals. Decrease in airway diameter can be accompanied by symptoms like breathlessness, cough, wheezing, chest tightness, and/or breathlessness on exertion. Management of asthma and COPD is generally directed towards the abnormal physiology and its sequelae. The main goals in managing asthma and COPD are: 1) to prevent or decrease airway narrowing, 2) to minimize the maximal level of airway narrowing, 3) to prevent or minimize increase in airflow limitation over time, and 4) to minimize symptoms.

Chapter 2 and 3 deal with the key lung function parameters of obstructive airways diseases: airways obstruction, bronchodilator responsiveness and bronchoconstrictor responsiveness. Long term effects of treatment on lung function, bronchoconstrictor responsiveness and symptoms are evaluated in chapter 4. The role of peak expiratory flow (PEF) measurements in disease management is discussed in chapter 5, 6, and 7, and finally, in chapter 8, the effects of a transdermally administrated anticholinergic agent on symptoms, lung function and bronchoconstrictor responsiveness to methacholine are described.

Chapter 2

In this chapter, the relation between bronchodilator and bronchoconstrictor responsiveness is discussed, as well as their supposed interchangeability in an epidemiological setting. Bronchodilator responsiveness has been considered the physiological opposite of bronchoconstrictor responsiveness in patients with obstructive airways diseases. As a consequence, bronchoconstrictor responsiveness tests have sometimes been replaced by bronchodilator responsiveness tests in epidemiological studies, especially in patients with obstructive airways, in order to prevent the risk of excessive airway narrowing. However, it can be questioned whether the outcome of both tests can be interchanged.

In this population based study, cumulative dose response curves were used for both tests. This allowed us to correlate the sensitivity to the constrictor (histamine) not only with the maximal airway dilatation (which is commonly performed) but also with the sensitivity to the bronchodilator (terbutaline).

Results show that bronchodilator and bronchoconstrictor responsiveness were not closely correlated, not even in a selection of subjects with airways obstruction. Patients with a bronchodilator response were not more likely to exhibit a

bronchoconstrictor response and the other way around. In a subgroup of subjects with a bronchoconstrictor response, sensitivity to histamine was correlated with sensitivity to terbutaline but not with the maximal airways response to terbutaline. From this study it can be stated that, in epidemiological research, the outcome of a bronchodilator test is not an accurate basis for the classification of a person as having increased responsiveness to a bronchoconstrictor. Bronchoconstrictor responsiveness and bronchodilator responsiveness are two different phenotypic markers that are not interchangeable in epidemiological studies.

Chapter 3

Hyperresponsiveness to a bronchoconstrictor is associated with airway inflammation in asthma. Bronchoconstrictor responsiveness can be tested with different stimuli such as methacholine (MCh) and adenosine 5'-monophosphate (AMP). MCh acts directly on airway smooth muscle and AMP acts directly on mast cells in the airway wall, resulting in release of mediators such as histamine, prostaglandines and leukotrienes. It has been shown before that inhaled corticosteroids improve bronchoconstrictor responsiveness to AMP more than to MCh. Furthermore, it is known that the long-acting β_2-agonist salmeterol protects against MCh induced bronchoconstriction equally well as the anti-inflammatory drug fluticasone. However, there were no data on the protective effect of salmeterol against AMP in comparison with fluticasone.

This study showed that bronchoconstrictor responsiveness to AMP was improved significantly more by maintenance treatment with fluticasone compared to salmeterol, 12 hours after the last dose (i.e. the moment at which the next dose should be taken). Salmeterol had a comparable protective affect against AMP and against MCh.

The larger protective effect of fluticasone to AMP compared to salmeterol might be explained by the influence of inhaled corticosteroids on the number and activity of the mast cells. The comparable protective effect of salmeterol against MCh and AMP might be explained by the fact that salmeterol is a very potent functional antagonist. Under treatment with salmeterol, a larger dose of a bronchoconstrictor is required to elicit a 20% fall in FEV_1.

In former studies, bronchoconstrictor responsiveness has been used as a major treatment-effect parameter in patients with asthma. With the conventional effect parameters (including bronchoconstrictor responsiveness to MCh) a comparable asthma controlling effect was observed for fluticasone and salmeterol. Our findings suggest that AMP challenge can serve better to discern the anti-inflammatory effects of inhaled corticosteroids from the functional antagonistic effects of long acting β_2-agonists in bronchoprovocation tests.

Chapter 4

Treatment with inhaled corticosteroids is widely used in management of patients with obstructive airways diseases. It has been shown that inhaled corticosteroids improve both airway diameter and bronchoconstrictor responsiveness. Until now, little is known about the duration of these improvements. In this chapter the long-term effects of treatment with inhaled beclomethasone in combination with terbutaline were evaluated in patients with increased bronchoconstrictor responsiveness and airways obstruction. In responders, the initial improvement in lung function, bronchial hyperresponsiveness and symptoms were well maintained over a total period of five years. Additionally, there was no accelerated fall in lung function in these patients compared to the general population.

Patients who did not respond sufficiently to beclomethasone 800 μg with respect to the FEV_1 showed no statistically significant improvement in FEV_1, bronchoconstrictor responsiveness, PEF, and symptoms after increasing the dose of BDP, although there was a trend toward improvement for all of these parameters. Because of the small number of nine insufficient responders, we could not draw firm conclusions from these results.

Our study stresses the importance of continuous long-term treatment with inhaled corticosteroids in patients with bronchial hyperresponsiveness and obstructive airways diseases.

Chapter 5

The role of PEF measurements in monitoring obstructive airways diseases has gained considerable importance since the appearance of the asthma treatment guidelines. Therefore, it is of great importance to test the reliability of PEF values obtained with frequently used PEF meters. In this study, we examined PEF values measured with peak flow meters that had been used more than 2,000 times over five years. We compared the PEF values of these (old) meters to values measured with identical new ones. In addition, accuracy of both old and new meters was assessed by pneumotachography.

We found a statistically significant, but for most patients clinically irrelevant difference in mean PEF value between old mini-Wright PEF meters and identical new meters. However, differences on an individual basis can be large. We concluded from this study that intensive and prolonged use of PEF meters does not lead to unreliable mean PEF values in long-term studies, and that replacement of PEF meters in disease monitoring or in long-term studies should be avoided, given the wide limits of agreement, except in case of obvious malfunction.

Chapter 6

Home PEF measurements have become the cornerstone of self-management plans. Treatment categories are defined on the basis of cut-off values of PEF, usually in three zones: green, yellow, and red. Entry into the lower PEF zones necessitates increased treatment. Unfortunately, to date the PEF cut-off values have been arbitrarily chosen.

In this chapter we evaluated the impact of advised PEF cut-off values on asthma treatment in clinically stable patients with increased bronchoconstrictor responsiveness and with a bronchodilator response. We have specifically focused on the prevalence of overtreatment in relation to these cut-off values. We also investigated how effects on overtreatment changed when using different criteria for the personal best value.

Strict adherence to advised cut-off values (80 and 60% of the personal best or of the predicted value) leads to a high prevalence of overtreatment in asthmatics who were treated with inhaled corticosteroids. Up to 30% of clinically stable patients would cross into the red zone at least once a year when personal best is the denominator and when it has not been limited to a defined time of the day or to defined prior bronchodilator use. A general lowering of cut-off values would certainly temper overtreatment, but is a rather crude solution and could lead to dangerous undertreatment. A better solution to our opinion is to relate measured peak flows to personal best values measured at the same time of the day and under the same conditions. It is obvious that when morning PEF values before the use of a bronchodilator (usually the lowest day value) are related to a personal best value measured in the evening after a bronchodilator (usually the highest day value) this will lead to frequent crossing into the yellow or red zones.

Morning PEF before medication seems to be the most useful parameter in self-management plans because this value is least influenced by variable prior use of bronchodilators.

We have focused entirely on overtreatment whereas the guidelines have been perceived (but not tested) in an era of concern about undertreatment. The final choice of the right cut-off value should be based on minimising both overtreatment and undertreatment. From the perspective of overtreatment, we suggest to use the morning value of PEF, expressed as % of the morning personal best value, at two consecutive days, being 50% for reaching the red zone and 70% for reaching the yellow zone. These morning PEF measurements should be performed before use of bronchodilators.

Chapter 7

Recent studies have shown that PEF indices like morning PEF and PEF variability correlate well with bronchoconstrictor responsiveness, cross-sectionally. Since bronchoconstrictor responsiveness is an important treatment parameter in asthmatic patients it would be desirable to have a PEF index that correlates well with bronchoconstrictor responsiveness, longitudinally.

In this 2-year study we evaluated which PEF index correlated best with bronchoconstrictor responsiveness longitudinally in patients with established increased bronchoconstrictor responsiveness, who started treatment with bronchodilators only or in combination with inhaled corticosteroids.

Changes in PEF indices reflecting bronchodilator response and within day variability correlated best with changes in bronchial hyperresponsiveness, but median rho values were low and varied only between -0.33 and -0.50. These results applied to the group of asthmatic patients, treated with inhaled corticosteroids and bronchodilators. In a similar group of patients who were treated with bronchodilators only, the median correlation coefficients were even lower.

Since it has been shown that PEF readings are inaccurate in certain flow ranges, we had hoped that the generally weak correlation coefficients between PEF indices and BHR would improve after correcting the PEF data for this inaccuracy. Unfortunately, there were no changes in correlation coefficients of any importance.

Because we only found weak to moderate correlations between PEF indices and bronchoconstrictor responsiveness longitudinally, we concluded that follow up of PEF indices are not a good proxy for changes in bronchoconstrictor responsiveness.

Chapter 8

Long-acting β_2-agonists have been developed to increase the duration of treatment effect. This is especially useful during the night when lung function values are low. Up to now there are no long-acting anticholinergic agents registered for patient use. It seems to be worthwhile to investigate transdermal delivery of bronchodilators because it produces sustained, constant and controlled plasma drug concentrations. Moreover, transdermal delivery might be accompanied by reduction in dose frequency, and thus increase patient compliance. In this chapter we combined two consecutive double-blind placebo-controlled cross-over studies on transdermal scopolamine (Scopoderm® TTS patches), an anticholinergic agent marketed for the prevention of nausea and vomiting associated with motion sickness.

In the first study, no significant effects of transdermal scopolamine on pulmonary function and symptoms were found. Nevertheless, there was a decrease in use of bronchodilators and a larger decrease in symptoms during daytime with scopolamine compared to placebo, though not statistically significant. The lack of clinical effect

was not due to inadequate uptake of scopolamine from the patch as shown by the urinary and plasma levels of scopolamine, but could be due to sub-therapeutic doses. The second study, however, demonstrated that a double dose of scopolamine was not able to improve clinical parameters further. There also was no significant protection of scopolamine to the responsiveness to methacholine. Unfortunately, the plasma levels of free scopolamine obtained with the two patches turned out to be sufficient to trigger a number of unwanted anticholinergic side effects, but were still too low to reach therapeutic levels at the cholinergic receptor sites in the lungs.

Conclusions

- Bronchoconstrictor responsiveness and bronchodilator responsiveness are two different phenotypic markers that are not interchangeable in epidemiological studies (chapter 2).
- In subjects with a bronchoconstrictor response, there is a weak but significant positive correlation between the sensitivity to the bronchoconstrictor histamine and the bronchodilator terbutaline (chapter 2).
- AMP challenges can serve better than MCh challenges to discern the anti-inflammatory effects of inhaled corticosteroids from the functional antagonistic effects of long acting β_2-agonists in bronchoprovocation tests (chapter 3).
- Mean initial improvements in lung function, bronchial hyperresponsiveness and symptoms are well maintained over at least five years in a group of patients who are treated with beclomethasone in combination with terbutaline (chapter 4).
- Intensive and prolonged use of mini-Wright PEF meters does not lead to unreliable mean PEF values in long term studies. Replacement in disease monitoring or in long-term studies should be avoided, given the wide limits of agreement (chapter 5).
- Currently advised PEF cut-off values in clinically stable asthmatics lead to overtreatment in substantial numbers of patients (chapter 6).
- Although PEF indices have been proven to be useful in self-management plans, they are not suitable as a proxy for bronchoconstrictor responsiveness longitudinally (chapter 7).
- The level of free scopolamine (obtained with two Scopoderm® TTS patches) is sufficient to trigger a number of unwanted anticholinergic side effects, but is too low to reach therapeutically effective levels at the cholinergic receptor sites in the lungs (chapter 8).

Recommendations for future research

In recent years, research on the management of obstructive airways diseases has made considerable progress. An important step forward was the introduction of inhaled corticosteroids. These drugs have become the mainstay of treatment regimes in patients with asthma. Another step was the introduction of self-management plans. With these plans, patients (especially asthmatics) gain more insight in their disease, and according to specific schemes they are encouraged to adjust their medication, based on defined criteria regarding symptoms and PEF values. The introduction of these plans could be labelled a little premature since the criteria on which treatment adjustments were based had not been studied properly. On the other hand, since they were written down, these plans have triggered off research to better document the use of PEF meters at home and their value in disease management (chapter 5 and 6).

Optimal individual dose of inhaled corticosteroids

Asthma is a chronic disease and it is, therefore, insufficient to be satisfied with short term improvement only. Improvements in short-term studies should subsequently be evaluated in studies with a long-term follow-up. Our study showed that treatment with inhaled corticosteroids in combination with β_2-agonists improved lung function, bronchoconstrictor response, and symptoms, and that the mean initial improvement of these parameters was well maintained over at least five years in patients with obstructive airways diseases (chapter 4). The results of this study applied to the group as a whole. However, for clinical practice and in self-management programs it is important to determine the optimal individual dose in order to avoid both undertreatment and overtreatment. Further studies are necessary to find a practicable strategy for adjustment of treatment. For example, one could start from the best possible personal situation with regard to the effect parameters. From that point, the dose of inhaled corticosteroids should be decreased without allowing deterioration of these parameters. An important issue of future research should be to find the most suitable parameters to predict deterioration in time. Ideally these parameters should also assess whether the physiology of the airway has normalized, i.e. the chronic sequelae of the inflammatory process.

Selection and definition of parameters

The choice and definition of the treatment-effect parameters and parameters of disease outcome is crucial in management plans. Many parameters of lung function, symptoms and bronchoconstrictor responsiveness are associated with obstructive airways diseases and most of these are not mutually interchangeable so that they seem to have their own place in relation to the disease. It would be preferable to find/select

only a few parameters, or a combination of parameters, that correlate best with the severity of the disease.

Effect parameters

In current guidelines on asthma management, adjustments of the level of anti-inflammatory treatment is based on changes in symptoms, lung function parameters and number or severity of exacerbations. Recently it has been shown that adjustment of the level of anti-inflammatory therapy should also be based on the outcome of repeated bronchoconstrictor tests.

To date, bronchoscopy (biopsy and bronchoalveolar lavage) is the golden standard to assess the inflammatory state of the airways. It is obvious that this investigation is not suitable in monitoring patients. Bronchoconstrictor tests are less invasive and are associated with inflammation. Unfortunately, these tests do also have some disadvantages. They can only be performed in a clinical setting because of possible excessive airway narrowing and possible side effects. Patients with cardiovascular diseases and/or a baseline FEV_1 less than 1 l. are usually excluded from these tests. Because of these disadvantages, it would be favourable to find a more suitable parameter to reflect inflammation. Our study showed that a bronchoconstrictor test can not be replaced by a bronchodilator test (chapter 3) and that none of the known PEF indices can be used as a proxy for bronchoconstrictor responsiveness, longitudinally (chapter 7). Future research might be able to find a parameter reflecting airway inflammation which can be easily obtained and interpreted, preferably in the home setting in that this parameter can also be used in self-management plans. One might think of a marker of airway inflammation in blood or sputum or exhaled air which could be measured at home by using reagent strips or instruments for readings, as is currently being used in diabetes self-measurements.

Disease outcome parameters

Examples of disease outcome parameters that are presently used include lung function parameters (prevention of an excessive decline in lung function and prevention of the development of irreversible airways obstruction), bronchoconstrictor responsiveness (improvement in bronchoconstrictor responsiveness as a proxy for the inflammatory state), number and severity of exacerbations and quality of life. One can argue whether one should aim for improvement in bronchoconstrictor response. Improvement in bronchoconstrictor responsiveness does not inevitably reflect improvement of inflammation. A similar improvement in bronchoconstrictor responsiveness to the same agonist, due to different treatments can be based on different underlying mechanisms, such as reduction in airway wall thickness, number and activity of inflammatory cells, or

airway smooth muscle dilatation (chapter 3). Further studies are necessary to investigate whether the same improvement in lung function, symptoms, number of exacerbations and bronchoconstrictor response, reached by different treatment regimens (long-acting bronchodilators or anti-inflammatory treatment) would have a similar disease outcome on the long term. It is likely that treatment aiming at improvement of airway inflammation will be preferable. This study showed that AMP challenges compared to MCh challenges can serve better to discern the anti-inflammatory effects of inhaled corticosteroids from the functional antagonistic effects of long-acting β_2-agonists in bronchoprovocation tests (chapter 3). Future long-term studies preferably should use both MCh and AMP challenges to investigate whether these tests have different predictive values with regard to disease outcome on the long term.

Transdermal delivery of anticholinergics

This study showed that two Scopoderm® TTS patches did not improve lung function and symptoms and had no protective effect against the bronchoconstrictor methacholine (chapter 8). Further research on transdermal application of anticholinergics should use a drug with a higher binding affinity to the muscarinic receptor sites in the lungs than to those in the central nervous system, responsible for the side effects. However, the need for transdermally administration in order to have a long duration of action reduces since long-acting anticholinergics with brondilation up to 48 hours after a single dose have entered phase 3 studies with promising results. At this point in time, it is a matter of speculation whether these long-acting anticholinergics will have a role in asthma, for instance in severe asthma and for patients with a fixed obstructive component despite the use of β_2-agonists.